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## **Interventions to support female BRCA mutation carriers who have undergone risk reducing surgery - protocol**

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# Interventions to improve psychosocial well-being in female *BRCA*-mutation carriers following risk-reducing surgery

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To examine psychosocial interventions in female *BRCA* carriers who have undergone risk-reducing surgery, and to evaluate the effectiveness of such interventions on QoL and emotional well-being.

## BACKGROUND

Hereditary breast and ovarian cancer (HBOC) is a syndrome that increases the risk of developing breast and ovarian cancer. It is estimated that up to 10% of invasive breast cancers are inherited, most of which are associated with the *BRCA1* and *BRCA2* genes (King 2003). Up to 1 in 6 (15%) of women diagnosed with ovarian cancers may have an inherited pathogenic *BRCA* mutation. NHS England has reported that this gene mutation accounts for 1020 of the 6800 cases of ovarian cancer diagnosed annually in the UK (NHS England 2015). These familial breast cancer genes have garnered attention since individuals of public interest have revealed their personal decisions to undergo risk-reducing surgery for breast or ovarian cancer, or both, because of a family history of these cancers and a positive gene status (Evans 2015). Raising the public profile of inherited breast and ovarian cancer has resulted in substantial increases in referrals to cancer genetics ser-

vices throughout the UK (Evans 2015; Foster 2007; Rosenberg 2016; Watson 2004). This exposure, alongside factors that have increased availability of genetic testing, such as Next Generation Sequencing (NGS) and updated National Institute for Health and Care Excellence (NICE) guidelines on genetic testing in families with HBOC (NICE 2013), has influenced perception and uptake of genetic testing. Prior to genetic testing for *BRCA* genes, which remains the most powerful tool for determining which individuals within a family are at risk (Euhus 2015), genetic counselling is offered where trained genetic counsellors can facilitate testing in a number of ways including discussion of family history, possible test outcomes, implications of the genetic test result and risk management options (Stan 2013). Current NICE guidance sets out the classification, care and management of familial breast cancer and related risks in people with a family history of breast cancer and defines those whose risk warrants a specialist genetic consul-

tation (NICE 2013).

## Description of the condition

Women who carry a pathogenic *BRCA* mutation are considered to have a significantly increased cumulative lifetime risk of developing breast cancer (40% to 85%) and risk of ovarian cancer (11% to 65%) (Antoniou 2003; den Heijer 2012; Ford 1998; King 2003), compared to women in the general population where risk for breast and ovarian cancer is 12% and 1.3% respectively (Chen 2007). While it is acknowledged that published estimates vary depending on study design, analyses and populations studied (Hartmann 2016), multiple other factors such as age of diagnosis of cancer in the index family member, type of cancer, family history of cancer and lifestyle factors contribute to this variation in risk (Mavaddat 2013). The Epidemiological Study of *BRCA1* and *BRCA2* mutation carriers (EMBRACE), one of the largest prospective studies collaborating with 28 centres across the UK and Ireland, discriminated between the two *BRCA* genes. The estimated cumulative lifetime risks, up to 70 years of age, for women with a *BRCA1* mutation are 60% risk of breast cancer, 59% for ovarian cancer and 83% for a contralateral breast cancer; for women with a *BRCA2* mutation risks were estimated as 55% for breast cancer, 16.5% for ovarian cancer and 62% for contralateral breast cancer (Mavaddat 2013).

Following confirmation of a pathogenic *BRCA* mutation women are faced with difficult choices of how best to manage their risk of developing breast or ovarian cancer. Options to consider are: enhanced surveillance with magnetic resonance imaging (MRI), mammogram and CA125 blood test, and a transvaginal ultrasound scan of the ovaries and fallopian tubes; risk-reducing surgery to their breast tissue or removal of their ovaries and fallopian tubes, or both; chemoprevention; and lifestyle interventions. A current Cochrane protocol references the need for international guidelines in *BRCA* testing in women with ovarian cancer and other cancers to facilitate consistent screening practices (Eleje 2016). The United Kingdom Familial Ovarian Cancer Screening Study (UK-FOCCS) has recently published data on screening in women who are at high risk for ovarian and fallopian tube cancer. It concluded that screening should not be viewed as an alternative to surgery, but it does seem to offer a better chance of avoiding a diagnosis of advanced incompletely resectable ovarian cancer or fallopian tube cancer, or both, in the interim (Rosenthal 2017).

Given the high risks of breast and ovarian cancer associated with the *BRCA* genes, many women choose to undergo risk-reducing mastectomy or risk-reducing bilateral salpingo-oophorectomy (RRBSO), or both, to maximise survival (Jeffers 2014). It is reported that 18% to 40% of women with a *BRCA* gene mutation will opt for risk-reducing mastectomy (Euhus 2015), with the higher percentage reported in the UK (Euhus 2015; Gopie 2013). Approximately 60% of women between the ages of 35 to 70 years who are *BRCA* carriers will elect to undergo RRBSO (Finch 2013).

Prospective studies report a 93% reduction in breast cancer risk for women who undergo risk-reducing mastectomy (De Felice 2015). Similarly, RRBSO may reduce the risk of ovarian cancer by 85% to 90% and breast cancer risk by 40% to 70% in women who are *BRCA* carriers (ACOG 2009). While such surgical interventions have demonstrated increased overall survival for this population, surgery is life-changing and can impact women adversely at a psychological, psychosexual and emotional level (Hartmann 2016; Stan 2013). In general, women regard risk-reducing surgery as a positive experience and have a sense of relief at the substantial cancer risk reduction and improvement in survival (Metcalf 2004). However studies have shown that, despite this positive experience, women are faced with unexpected physical changes that affect the function and appearance of their bodies. These changes can have a negative impact on sexuality and relationships (Gahm 2013; Gopie 2013; Hallowell 2012). The focus of this Cochrane Review is the effectiveness of interventions on psychosocial outcomes and survival will not be part of the scope.

## Description of the intervention

Prior to genetic testing, women at risk of cancer are provided with genetic counselling by trained genetic counsellors or consultant geneticists, as directed by NICE guidance 164 (NICE 2013). Genetic counselling, as an activity, is “the process of helping people understand and adapt to the medical, psychological and familial implications of the genetic contributions to disease. The process includes interpretation, risk assessment, education and counselling” (Resta 2006). Specifically the role of the genetic counsellor, according to Skirton 2010, is as follows.:

- To identify the needs of the individual or family and use an empathic client-centred approach in the provision of genetic counselling.
- To collect, select, interpret and analyse information (including family and medical history, pedigree, laboratory results and literature) relevant to the delivery of genetic counselling for individuals or families.
- To help people understand and adapt to the medical, psychological, social and familial implications of genetic contributions to disease.
- To assess the chance of occurrence or recurrence; to provide education about inheritance, testing, management, prevention, resources and research to relevant individuals or families.
- To promote informed choices and psychological adaption to the condition or risk of the condition.
- To apply expert knowledge to facilitate the individual or family to access the appropriate healthcare resources, including a medical diagnosis and resources for management of the condition.

Women with a diagnosis of cancer may experience a different pathway due to the recent 'mainstreaming' of cancer genetics in some

areas in the UK and beyond (genetic testing outside of clinical genetics services). Women who have a diagnosis of cancer may access genetic testing at the time of diagnosis and the pre-test counselling is provided by oncologists. If a mutation is identified, these women can be referred to genetic services for further information and genetic counselling. Individuals who test positive for a *BRCA* mutation are not routinely followed up by the genetics service after their result disclosure consultation, but are referred on for screening and risk-reducing consultations with surgeons.

The extent of need for psychosocial support in women who are *BRCA* carriers and have undergone risk-reducing surgery has not been wholly quantified. However, retrospective and prospective studies have highlighted women's concerns and experiences (Brandberg 2008; den Heijer 2012; Gahm 2010; Metcalfe 2004; McGaughey 2006; van Oostrom 2003), with significant numbers of women reporting some adverse experience. Studies have reported on long-term follow up of *BRCA* carriers who had risk-reducing surgery. Studies have found that approximately one-third of women felt less feminine, with reported changes in sexual attractiveness (55%), feeling less physically attractive (53%) and self-consciousness about appearance (53%). Other concerns were related to surgical complications for which women received further psychiatric intervention (Hopwood 2000). Women without a diagnosis of cancer who underwent risk-reducing mastectomy felt embarrassed about their naked body (21%), were not satisfied with the appearance of reconstructed breasts (29%), but reported significant reduction in cancer-specific distress (Gopie 2013).

This Cochrane Review will focus on psychological, psychosexual and psychoeducational interventions provided to support female *BRCA* carriers after risk-reducing surgery, and the effectiveness of such interventions on quality of life (QoL) and the psychological consequences of risk-reducing surgical intervention. While there is no universal definition of QoL, it is used to describe general health status (Aaronsen 1998; Barofsky 2012). Interventions for this review will adhere to a previous Cochrane Review's definition of a psychosocial intervention as non-pharmacological, involving an interpersonal relationship between an individual, or group of individuals, and one or more trained (usually professional) helpers (Galway 2012).

### How the intervention might work

Genetic testing and the resulting medical decisions around risk reduction lead to a unique set of emotional, physical and sexual issues for women who are *BRCA* carriers (Matloff 2009). RRBSO results in surgically-induced menopause, which is related to significantly compromised sexual function (Bober 2015; Finch 2011; Robson 2003), for which there is little effective treatment. Studies have shown that psychosocial interventions have improved women's sexual difficulties (Bober 2015). Improvements in overall sexual functioning, including desire, arousal, satisfaction and pain, have been demonstrated using interventions that integrate elements of

cognitive behavioural therapy (CBT) with sexual health education and mindfulness meditation (Bober 2015). Similarly, mindfulness-based interventions in people with breast cancer have shown improvements in QoL and stress reduction (Lengacher 2009).

### Why it is important to do this review

While the literature recognises that risk-reducing procedures have a significant impact at a psychosocial level and can affect QoL, both at an individual level and that of the family (Brotto 2012; Finch 2013; Gopie 2013; Hallowell 2012; Jeffers 2014; Stan 2013), interventions to measure such concepts and outcomes in this population have yet to be systematically reviewed. Previous systematic reviews and meta-analyses have assessed the efficacy of psychological interventions in people attending sessions for sexual dysfunction (Frühau 2013). There has been an informative literature review on the influence of medical choices on QoL in unaffected *BRCA* carriers (Harmsen 2015). Given the developments in genetic testing and the increase in availability and uptake of testing, coupled with improved surgical techniques such as breast reconstruction, more women are choosing to undergo prophylactic bilateral mastectomy; a 12% annual increase over the last decade has been reported in the USA (Euhus 2015). Long-term follow-up studies on the impact of risk-reducing mastectomy have shown that women had ongoing difficulties with body image up to two to nine years after surgery (den Heijer 2012; Unukovich 2012). Studies have shown that sexual side effects are the most commonly cited areas of concern post-RRBSO for women who are *BRCA* gene carriers, yet 60% of the most common symptoms women experienced post-surgery had not been discussed before surgery (Campfield Bonadies 2011). Women need to be provided with information and supportive interventions to ensure they have the best psychological outcomes following their decision to undergo risk-reducing surgery. This review will identify the psychosocial care and management and impact on this cohort of women pre- and post-operatively.

## OBJECTIVES

To examine psychosocial interventions in female *BRCA* carriers who have undergone risk-reducing surgery, and to evaluate the effectiveness of such interventions on QoL and emotional well-being.

## METHODS

### Criteria for considering studies for this review

## Types of studies

Randomised controlled trials (RCTs), but these may be limited in number due to ethical considerations and the “nature of the clinical field” (Schouten 2016). If this is the case we will include the following types of studies.

- Quasi-randomised trials.
- Non-randomised trials, prospective and retrospective cohort studies.
- Interventional studies.
- Case control studies.

## Types of participants

Women, 18 years or older, who have tested positive for a pathogenic mutation in *BRCA1* or *BRCA2*, or both. All participants will have had risk-reducing surgery; either risk-reducing mastectomy or RRBSO, or both. Women may or may not have had a diagnosis of breast or ovarian cancer, or both.

## Types of interventions

These will include the following.

- Psychological interventions pre or post risk-reducing surgery, or both.
- Psychoeducational intervention pre or post risk-reducing surgery, or both.
- Psychosexual interventions pre or post risk-reducing surgery, or both.

We will compare any of these interventions with any other intervention or usual care.

## Types of outcome measures

### Primary outcomes

- QoL: improved QoL assessed at specified time points during or post-intervention, measured using a scale that has been validated through reporting of norms in a peer-reviewed publication such as Short Form-36 Health Survey (Ware 1998), or the cancer generic EORTC QLQ-C30 questionnaire (Fayers 2002).
- Psychological distress: such as anxiety, depression, cancer worry measured using a scale that has been validated through reporting of norms in a peer-reviewed publication, such as Impact of Event Scale (Horowitz 1979), the Beck Depression Inventory (Beck 1974), or the General Health Questionnaire (Goldberg 1979).

### Secondary outcomes

- Sexual functioning measured using a scale that has been validated through reporting of norms in a peer-reviewed publication, such as the Brief Symptom Inventory (Derogatis 1983), the Female Sexual Function Index (Rosen 2000), or the Female Sexual Distress Scale (Derogatis 2002).
- Body image measured using the Body Image Scale (Hopwood 2001).
- Psychosocial issues to include cognitive, emotional and spiritual.

We will include trials with different outcomes than those mentioned above provided they measure the same construct.

We will present a 'Summary of findings' table and will report the following outcomes listed in order of priority (see Data synthesis).

- Improved QoL.
- Psychological distress.
- Sexual functioning.
- Body image.
- Psychosocial well-being to include cognitive, emotional and spiritual components.

## Search methods for identification of studies

There will be no language restrictions for our searches. We will search for papers in all languages and translate to English as necessary.

### Electronic searches

To identify studies for inclusion in this review, we will develop detailed search strategies for each of the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, latest issue).
- MEDLINE (Ovid 1995 to date).
- Embase (1995 to date).
- CINAHL (1995 to date).
- PsycINFO (1995 to date).
- Web of Science (1995 to date).
- Scopus (1995 to date).

The MEDLINE search strategy is presented in Appendix 1. For databases other than MEDLINE Ovid, we will adapt the search strategy accordingly.

### Searching other resources

### Unpublished and grey literature

We will search other sources such as the following.



- USA National Cancer Institute (<https://www.cancer.gov/about-cancer/treatment/clinical-trials>).
- USA National Institutes of Health (<https://clinicaltrials.gov/ct>).
- ISRCTN registry ([www.isrctn.com/](http://www.isrctn.com/)).
- Dissertation and theses databases; [British Library EThOS](#).

### Handsearching

To try identify any unpublished studies we will handsearch the reference lists of included studies and previous systematic reviews. We will search conference abstracts from the following sources from 2010 to date.

- Association of Genetic Nurse Counsellors.
- Irish Society of Human Genetics.
- Cancer Genetics Spring Meeting.
- European Society of Human Genetics.
- International Psycho Oncology Society.
- American Psycho Oncology Society.
- Gynecologic Oncology (Annual meeting of the American Society of Gynecologic Oncologist).
- Annual Meeting of European Society of Medical Oncology (ESMO).
- American Society of Clinical Oncology.

### Data collection and analysis

#### Selection of studies

We will download all study titles identified by the searches into [Mendeley](#) and remove any duplicates. Two review authors (LJ and JR) will independently screen the keywords, titles and abstracts of electronic citations and exclude studies that clearly do not meet the inclusion criteria. Any disagreement will be resolved by communicating with all review authors. Following screening, we will obtain full-text copies of potentially relevant references. Two review authors (LJ and JR) will independently assess the eligibility for inclusion of the retrieved citations. If differences of opinion arise, we plan to seek the opinions of the other review authors (DF, PM and MD). If we need additional information to ascertain eligibility, we will contact the study authors. We will identify and exclude duplicate reports and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will document studies excluded after full-text assessment, giving reasons for exclusion in the 'Characteristics of excluded studies' table. We will record the selection process in sufficient detail to complete a PRISMA flow diagram.

### Data extraction and management

Two review authors (LJ and JR) will independently extract data from original reports using a data extraction form adapted for this review available from the Cochrane Effective Practice and Organisation of Care (EPOC) Group ([Cochrane EPOC 2013; Appendix 2](#)). We will resolve any disagreement by consensus between the two review authors or, where necessary, between all review authors (LJ, JR, DF, PM and MD).

We will use the adapted data extraction form for this review and, where possible, extract the following information from each included study.

- Author, year of publication and journal citation (including language).
- Country of origin.
- Aim and inclusion criteria.
- Study design, methodology.
- Study population:
  - the number of participants eligible;
  - participant characteristics;
  - age;
  - affected or healthy at risk;
  - type of cancer;
  - type of risk reducing surgery;
  - *BRCA1* or *BRCA2* mutation.
- Intervention details:
  - who delivered it;
  - duration and number of sessions;
  - mode of delivery;
  - content of intervention;
  - name of validated instruments.
- Outcomes:
  - definition of outcome;
  - time when outcome measured e.g. one month, six months post-surgery;
  - unit of measurement.
- Results:
  - the number of participants evaluated at follow-up;
  - reasons for loss to follow-up;
  - how each study handled missing responses if stated and the actual results;
  - QoL and secondary outcome measures final values and standard deviation (SD) of outcome;
  - record number of patients assessed at each endpoint in the treatment arm and at follow-up to estimate the mean difference (MD) between treatment arm and its standard error.

If we find more than one publication of the same study, we will use the most recent publication for data extraction and collate multiple reports of the same study as the unit of interest in the review.

### Assessment of risk of bias in included studies



## RCTs

Two review authors (LJ and JR) will independently assess the risk of bias of each included RCT using the Cochrane 'Risk of bias' assessment tool (Higgins 2011a).

This will include assessment of the following.

- Selection bias: this will include sequence generation and allocation concealment.
- Performance bias: we will assess performance bias (due to knowledge of the allocated interventions by participants and personnel during an RCT) by assessing if study participants and study personnel were blinded.
- Detection bias: we will assess that outcomes are assessed in a valid way such as the use of validated instruments for psychological measures and that they are applied to both groups.
- Attrition bias: we will assess the amount, type and handling of incomplete data to ensure dropouts or withdrawals of participants from studies are adequately accounted for. If less than 20% of the data is missing on the primary outcome, we will consider this to be low attrition bias; if 20% or more of data is missing, we will consider it to be high attrition bias; and if we cannot calculate the percentage of missing data, we will judge attrition bias as unclear.
- Reporting bias: selective reporting of outcomes.
- Other possible sources of biases.

## Non-randomised studies (NRS)

Two authors (LJ and JR) will assess the risk of bias of each included NRS using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool (Sterne 2016). For reaching 'Risk of bias' judgements in ROBINS-I: pre-intervention and at-intervention domains see Table 1.

## Measures of treatment effect

### Dichotomous data

We will analyse dichotomous outcomes by calculating the risk ratio (RR) for each included study. We will express uncertainty in each result using 95% confidence intervals (CIs).

### Continuous data

We will use mean differences if outcome measures on all studies included in the review are made on the same scale. It is unlikely that most psychosocial studies use the same measurement scale to assess QoL and emotional well-being and related constructs, and in that case we will use the standardised mean difference (SMD). We will calculate effect sizes on the basis of means, SDs and sample sizes for each study condition. We will analyse the standard error by number of patients in the treatment arm and the number of patients at endpoints.

## Unit of analysis issues

### Repeated observations on participants

If there are longitudinal designs with repeated observations on participants, we will define several outcomes based on different periods of follow-up and conduct separate analyses, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). One analysis will include all studies with measurement at the end of intervention (post-test), and we will base other analyses on the period of follow-up (short-term: three months or less; medium-term: more than three to six months; and long-term follow-up: more than six months).

### Dealing with missing data

If data are missing, we will contact the study authors to request data on outcomes. We will not impute missing data for the primary outcomes.

### Assessment of heterogeneity

We expect some heterogeneity due to the clinical and methodological diversity. Heterogeneity between studies will be assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling error ( $I^2$  statistic) (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Chi<sup>2</sup> test) (Deeks 2001), and, if possible, by subgroup analyses. If there is no evidence of heterogeneity, we will use a fixed-effect model, which assumes a common underlying effect behind every trial. If there is evidence of substantial heterogeneity, we will investigate and report the possible reasons for this. If we suspect marked heterogeneity, we will not combine estimates. All potential causes of such heterogeneity will be explored through subgroup and sensitivity analysis. We will use a random-effects model if meta-analysis is appropriate; we will assume each trial to be measuring a different, true effect. While it is acknowledged that a random-effects model is more susceptible to publication bias, we will incorporate methods to formally test publication bias into the analysis as outlined below.

### Assessment of reporting biases

If appropriate (i.e. if the review includes more than 10 RCTs), we will examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small study effects such as publication bias. Additionally, we will explore possible sources of asymmetry in funnel plot, such as selective outcome reporting, poor methodological quality leading to spuriously inflated effects in smaller studies, true heterogeneity, artefactual and chance as outlined by Egger 1997. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by

the random-effects model, we will perform further meta-analysis using a fixed-effect model. If the review includes fewer than 10 RCTs, then we will use a qualitative assessment of reporting biases, whereby the authors will review and summarise the evidence from the RCTs.

### Data synthesis

This review will include both RCTs and NRS, if no RCTs are available. If sufficient, clinically similar studies are available, we will pool their results in meta-analyses using Review Manager 5 (RevMan 5) (RevMan 2014). We will use adjusted summary statistics if available; otherwise we will use unadjusted results. Where more than one adjusted effect is reported in a paper, we will use the estimate that is identified as the primary adjusted effect by study authors.

We will use random effects using invariance variance weighting for any meta-analysis.

For continuous outcomes, we will pool the mean differences between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale; otherwise we will pool the SMD. For any dichotomous outcomes, we will calculate the RR for each study and we will then pool these. The final discussion will include a narrative synthesis of the findings of each study design.

### Quality of the evidence

We will present the overall quality of the evidence for each outcome (see [Types of outcome measures](#)) according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). We will create a 'Summary of findings' table (Appendix 3) based on the methods described the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and using GRADEpro 2015. We will use the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We will downgrade the evidence from 'high' quality by one level for serious (or by two for very serious) for each limitation.

- High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

- Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

- Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

### Subgroup analysis and investigation of heterogeneity

We will not perform post hoc subgroup analysis. Where appropriate, we will undertake subgroup analysis, potentially grouping the trials by the following.

- Type of treatment regime (psychological, psychoeducational, psychosexual intervention).
- Duration of treatment (short term less than one month, longer term more than three months).
- Cancer diagnosis (affected women) or no cancer (healthy at risk women).
- Type of risk-reducing surgery; mastectomy or RRBSO.

### Sensitivity analysis

We will perform the following sensitivity analyses.

- Exclusion of studies that are at high risk of bias.
- Using unadjusted results.

If possible, we will conduct the analyses on an intention-to-treat basis. If this is not possible, we will use available case analysis. The sensitivity analysis will consider how the results would have differed for assumed means or event rates for missing data.

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\* Indicates the major publication for the study

## ADDITIONAL TABLES

Table 1. 'Risk of bias' judgements in ROBINS-I: pre-intervention and at-intervention domains

Judgement	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions
Low risk of bias: the study is comparable to a well-performed RCT with regard to this domain	No confounding expected	(i) All participants who would have been eligible for the target trial were included in the study; and (ii) for each participant, start of follow-up and start of intervention coincided	i) Intervention status is well-defined; and (ii) intervention definition is based solely on information collected at the time of intervention
Moderate risk of bias: the study is sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well-performed randomised trial	i) Confounding expected, all known important confounding domains appropriately measured; and (ii) reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding	Selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; or (ii) start of follow-up and start of intervention do not coincide for all participants; and (a) the proportion of participants for which this was the case was too low to induce important bias; or (b) the authors used appropriate methods to adjust for the selection bias; or the review authors are confident that the rate (hazard) ratio for the effects of intervention remains constant over	(i) Intervention status is well-defined; and (ii) some aspects of the assignments of intervention status were determined retrospectively

**Table 1. 'Risk of bias' judgements in ROBINS-I: pre-intervention and at-intervention domains** (Continued)

		time	
Serious risk of bias: the study has some important problems	(i) At least one known important domain was not appropriately measured, or not controlled for; or (ii) reliability or validity of measurement of an important domain was low enough that we expect serious residual confounding	(i) Selection into the study was related (but not very strongly) to intervention and outcome, and this could be adjusted for in analyses; or (ii) start of follow-up and start of intervention do not coincide, a potentially important amount of follow-up time is missing from analyses, and the rate ratio is not constant over time	i) Intervention status is not well-defined; or (ii) major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome
Critical risk of bias: the study is too problematic to provide any useful evidence on the effects of intervention	(i) Confounding inherently not controllable; or (ii) the use of negative controls strongly suggests unmeasured confounding	(i) Selection into the study was very strongly related to the intervention and outcome and this could be adjusted for in analyses; or (ii) a substantial amount of follow-up time is likely to be missing from analyses, and the rate ratio is not constant over time.	Unusual: an extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases
No information on which to base a judgement about risk of bias for this domain	No information on whether confounding might be present	No information is reported about selection of participants into the study or whether start of follow-up and start of intervention coincide	No definition of the intervention or no explanation of the source of information about intervention status is reported

## APPENDICES

### Appendix I. MEDLINE search strategy

1. Genes, BRCA1/
2. BRCA1 Protein/
3. Genes, BRCA2/
4. BRCA2 Protein/
5. (BRCA\* or brca\*).mp.
6. ((BRCA\* or brca\*) adj5 (carrier\* or tumor\* or tumour\* or gene\* or suppress\* or protein\* or mutat\* or alter\* or damage\* or inherit\* or heredit\*)).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Prophylactic Surgical Procedures/
9. exp Mastectomy/



10. Ovariectomy/
11. surgery.fs.
12. ((risk reduc\* or prophylactic) adj5 (surg\* or mastectom\* or RRM or ovar\* or RRBSO or BSO or bilateral salpingo-oophorectom\* or oophorectomy\* or interven\*)).mp.
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13
15. randomized controlled trial.pt.
16. controlled clinical trial.pt.
17. randomized.ab.
18. placebo.ab.
19. randomly.ab.
20. trial.ti.
21. groups.ab.
22. exp cohort studies/
23. exp case-control studies/
24. (cohort\* or prospective\* or retrospective\* or (case\* and (control\* or series))) .mp.
25. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. (animals not (humans and animals)).sh.
27. 25 not 26
28. 14 and 27

Key  
[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

## Appendix 2. Data extraction form

### Review title or ID

- Study ID (surname of first author and year first full report of study was published e.g. Smith 2001).
- Report IDs of other reports of this study (e.g. duplicate publications, follow-up studies).
- Notes.

### General information

- Date form completed (dd/mm/yyyy).
- Name/ID of person extracting data.
- Report title (title of paper/ abstract/ report that data are extracted from).
- Report ID (if there are multiple reports of this study).
- Country of origin.
- Publication type (e.g. full report, abstract, letter).
- Study funding source (including role of funders).
- Possible conflicts of interest (for study authors).
- Notes.

### Eligibility

#### Study characteristics

- Review inclusion criteria (insert inclusion criteria for each characteristic as defined in the protocol): Yes/No/Unclear.
- Location in text (page and paragraph/figure/table).
- Type of study.

- Randomised trial /non-randomised trial.
- Other design (specify).
- Participants.
- Types of intervention.
- Types of outcome measures.
- Decision.
- Reason for exclusion.
- Notes.

## **Do not proceed if study excluded from review**

### **Population and setting**

- Description.
- Include comparative information for each group (i.e. intervention and controls) if available.
- Location in text (page and paragraph/figure/table).
- Population description (from which study participants are drawn).
- Setting (including location and social context).
- Inclusion criteria.
- Exclusion criteria.
- Method(s) of recruitment of participants.
- Notes.

### **Methods**

- Descriptions as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Study aim.
- Design (e.g. parallel, crossover, non-RCT).
- Start date.
- End date.
- Duration of participation (from recruitment to last follow-up).
- Notes.

### **'Risk of bias' assessment**

See Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). Additional domains may be required for non-randomised studies.

### **Domain**

- Risk of bias: low/high/unclear:
  - support for judgement;
  - location in text (page and paragraph/figure/table);
  - random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias):
  - outcome group: all/(if required);
  - outcome group.
- Blinding of outcome assessment (detection bias):
  - outcome group: all/(if required);
  - outcome group.

- Incomplete outcome data (attrition bias).
- Selective outcome reporting? (reporting bias).
- Other bias.
- Notes.

## Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Total number randomised (or total population at start of study for NRCTs).
- Clusters (if applicable, number, type, number people per cluster).
- Baseline imbalances.
- Withdrawals and exclusions (if not provided below by outcome).
- Age.
- Sex.
- Race/ethnicity.
- Subgroups measured.
- Cancer (Y/N).
- Type of cancer.
- Risk-reducing mastectomy.
- RRBSO.
- *BRCA1* or *BRCA2*.
- Subgroups reported.
- Notes.

## Intervention groups

(Copy and paste table for each intervention and comparison group)

- Intervention Group 1.
- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Group name.
- Number randomised to group (specify whether number of people or clusters).
- Description (include sufficient detail for replication, e.g. content, dose, components; if it is a natural experiment, describe the pre-intervention).
- Duration of treatment period.
- Timing (e.g. frequency, duration of each episode).
- Delivery (e.g. mechanism, medium, intensity, fidelity).
- Providers (e.g. number, profession, training, ethnicity etc. if relevant).
- Co-interventions.
- Notes.

## Outcomes

(Copy and paste table for each outcome)

- Outcome 1.
- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Outcome name.
- Time points measured (specify whether from start or end of intervention).
- Time points reported.

- Outcome definition (with diagnostic criteria if relevant and note whether the outcome is desirable or undesirable if this is not obvious).
- Person measuring/reporting.
- Unit of measurement (if relevant).
- Scales: upper and lower limits (indicate whether high or low score is good).
- Is outcome/tool validated? Yes/No/Unclear.
- Imputation of missing data (e.g. assumptions made for ITT analysis).
- Notes.

## Results

(Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required)

### For randomised or non-randomised trial: dichotomous outcome

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Comparison.
- Outcome.
- Subgroup.
- Time point (specify whether from start or end of intervention).
- Note whether: post-intervention or change from baseline.
- Adjusted.
- Unadjusted.
- Intervention.
- Comparison.
- Number of events.
- Number of participants.
- Number of events.
- Number of participants.

### Baseline data

- Intervention.
- Comparison
- Number of events.
- Number participants.
- Number of events.
- Number of participants.
- Number of missing participants and reasons.
- Number of participants moved from other group and reasons.
- Any other results reported.
- Unit of analysis (e.g. by individuals, health professional, practice, hospital, community).
- Statistical methods used and appropriateness of these methods (e.g. adjustment for correlation).
- Notes.

### For randomised or non-randomised trial : continuous outcome

- Description as stated in report/paper:
  - location in text (page and paragraph/figure/table);
  - comparison;
  - outcome;

- subgroup;
- time point (specify whether from start or end of intervention);
- post-intervention or change from baseline;
- results;
  - ◇ note whether: post-intervention or change from baseline;
  - ◇ and whether adjusted or unadjusted;
  - ◇ intervention;
  - ◇ comparison;
  - ◇ mean;
  - ◇ SD (or other variance);
  - ◇ number of participants;
  - ◇ mean;
  - ◇ SD (or other variance);
  - ◇ number of participants.

### ***Baseline data***

- Intervention.
- Comparison.
- Mean.
- SD (or other variance).
- Number of participants.
- Mean.
- SD (or other variance).
- Number of participants.
- Number of missing participants and reasons.
- Number of participants moved from other group and reasons.
- Any other results reported.
- Unit of analysis (e.g. by individuals, health professional, practice, hospital, community).
- Statistical methods used and appropriateness of these methods (e.g. adjustment for correlation).
- Notes.

### **For randomised or non-randomised trial: other outcome**

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Comparison.
- Outcome.
- Subgroup.
- Time point (specify whether from start or end of intervention).
- Type of outcome.
- Results:
  - intervention result;
  - SD (or other variance);
  - control result;
  - SD (or other variance);
  - overall results;
  - SE (or other variance);
  - number of participants;
  - intervention;
  - control;
  - number of missing participants and reasons;

- number of participants moved from other group and reasons;
- any other results reported;
- unit of analysis (e.g. by individuals, health professional, practice, hospital, community);
- statistical methods used and appropriateness of these methods;
- Notes:

#### **For controlled before-after study**

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Comparison.
- Outcome.
- Subgroup.
- Timepoint (specify whether from start or end of intervention).
- Post-intervention or change from baseline.
- Results:
  - intervention result;
  - SD (or other variance);
  - control result;
  - SD (or other variance);
  - overall results;
  - SE (or other variance);
  - No. participants;
  - intervention;
  - control;
  - number of missing participants and reasons;
  - number of participants moved from other group and reasons;
  - any other results reported;
  - unit of analysis (individuals, cluster/ groups or body parts);
  - statistical methods used and appropriateness of these methods.
- Notes.

#### **For interrupted time series or repeated measures study**

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Comparison.
- Outcome.
- Subgroup.
- Length of timepoints measured (e.g. days, months).
- Total period measured.
- Number of participants measured.
- Number of missing participants and reasons.
- Number of timepoints measured.
- Pre-intervention.
- Post-intervention.
- Mean value (with variance measure).
- Difference in means (post- and pre-intervention).
- Percent relative change.
- Result reported by authors (with variance measure).
- Unit of analysis (individuals or cluster/groups).
- Statistical methods used and appropriateness of these methods.
- Notes.

### Applicability

- Does the study directly address the review question? (any issues of partial or indirect applicability): Yes/No/Unclear.
- Notes.

### Other information

- Description as stated in report/paper.
- Location in text (page and paragraph/figure/table).
- Key conclusions of study authors.
- References to other relevant studies.
- Correspondence required for further study information (what and from whom).
- Further study information requested (from whom, what and when).
- Correspondence received (from whom, what and when).
- Notes

## Appendix 3. Draft 'Summary of findings' table

Interventions to improve psychosocial well-being in female <i>BRCA</i> -mutation carriers following risk-reducing surgery						
<b>Patient or population:</b> adult women, 18 years or older, who have tested positive for a pathogenic mutation in <i>BRCA1</i> or <i>BRCA2</i> , or both and had risk-reducing surgery						
<b>Settings:</b> outpatient						
<b>Intervention:</b> psychosocial interventions designed to improve quality of life (QoL)						
<b>Comparison:</b> no intervention						
Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
Improved QoL						
Psychological distress						
Sexual functioning						
Body image						
Psychosocial well-being						
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Abbreviations: CI: confidence interval; QoL: quality of life						



(Continued)

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**GRADE Working Group grades of evidence**

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

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## **CONTRIBUTIONS OF AUTHORS**

All authors read and approved the final protocol draft.

Lisa Jeffers: Conceptualising the topic for the review, drafting the protocol, developing the search strategy.

Joanne Reid: Reviewing and editing the protocol.

Donna Fitzsimons: Reviewing and editing the protocol.

Patrick J Morrison: Reviewing and editing the protocol.

Martin Dempster: Reviewing and editing the protocol.

## **DECLARATIONS OF INTEREST**

Lisa Jeffers: none known

Joanne Reid: none known

Donna Fitzsimons: none known

Patrick J Morrison: none known

Martin Dempster: none known

## **SOURCES OF SUPPORT**

### **Internal sources**

- No internal sources of support, Other.

## External sources

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